VALUE IN HEALTH 16 (2013) 973–986

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Cost-Effectiveness of Boceprevir in Patients Previously Treated for Chronic Hepatitis C Genotype 1 Infection in the United States

Jagpreet Chhatwal, PhD[1,2,], Shannon A. Ferrante, PhD[2], Cliff Brass, MD, PhD[2,3], Antoine C. El Khoury, PhD[2], Margaret Burroughs, MD[2], Bruce Bacon, MD[4], Rafael Esteban-Mur, MD[5], Elamin H. Elbasha, PhD[2]*

[1]*Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA;* [2]*Merck, Sharp, & Dohme Corp., Whitehouse Station, NJ, USA;* [3]*Novartis, East Hanover, NJ, USA;* [4]*Saint Louis University School of Medicine, St. Louis, MO, USA;* [5]*Servei de Medicine Interna-Hepatologia, Valle Hebron Hospital, Barcelona, Spain*

ABSTRACT

Objectives: The phase 3 trial, Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol-2 (RESPOND-2), demonstrated that the addition of boceprevir (BOC) to peginterferon-ribavirin (PR) resulted in significantly higher rates of sustained virologic response (SVR) in previously treated patients with chronic hepatitis C virus (HCV) genotype-1 infection as compared with PR alone. We evaluated the cost-effectiveness of treatment with BOC in previously treated patients with chronic hepatitis C in the United States using treatment-related data from RESPOND-2 and PROVIDE studies. **Methods:** We developed a Markov cohort model to project the burden of HCV disease, lifetime costs, and quality-adjusted life-years associated with PR and two BOC-based therapies—response-guided therapy (BOC/RGT) and fixed-duration therapy for 48 weeks (BOC/PR48). We estimated treatment-related inputs (efficacy, adverse events, and discontinuations) from clinical trials and obtained disease progression rates, costs, and quality-of-life data from published studies. We estimated the incremental cost-effectiveness ratio (ICER) for BOC-based regimens as studied in RESPOND-2, as well as by patient's prior response to treatment and the IL-28B genotype. **Results:** BOC-based regimens were projected to reduce the lifetime incidence of liver-related complications by 43% to 53% in comparison with treatment with PR. The ICER of BOC/RGT in comparison with that of PR was $30,200, and the ICER of BOC/PR48 in comparison with that of BOC/RGT was $91,500. At a willingness-to-pay threshold of $50,000, the probabilities of BOC/RGT and BOC/PR48 being the preferred option were 0.74 and 0.25, respectively. **Conclusions:** In patients previously treated for chronic HCV genotype-1 infection, BOC was projected to increase quality-adjusted life-years and reduce the lifetime incidence of liver complications. In addition, BOC-based therapies were projected to be cost-effective in comparison with PR alone at commonly used willingness-to-pay thresholds.

Keywords: hepatitis C, Markov model, protease inhibitor.

Introduction

Chronic infection with hepatitis C virus (HCV) is a major public health problem, with more than 170 million people infected worldwide [1,2]. In the United States, chronic HCV infection is a leading cause of chronic liver diseases and hepatocellular carcinoma (HCC), and is the most common indication for liver transplantation [1]. In 2007, there were 15,000 deaths related to HCV infection in the United States, surpassing the nearly 13,000 deaths caused by HIV infection [3].

Of the six HCV genotypes, genotype 1 is the most prevalent in the United States and accounts for at least 70% of all chronic infections, followed by genotypes 2 and 3 (14% and 8%, respectively) [4]. HCV genotype 1 is also the most difficult to treat with a combination of peginterferon-ribavirin (PR)—less than 50% of treated patients achieve a sustained virologic response (SVR), which is the primary goal of the treatment. Response rates are even lower in nonresponders (15.6%, confidence interval [CI] 12.4%–19.4%) to previous PR therapy who are re-treated with PR [5].

Disclosure of Potential Conflicts of Interest: Dr. Chhatwal is a former employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, and has received consulting fees. Drs. Ferrante, El Khoury, Burroughs, and Elbasha are current employees of Merck and hold stock and/or stock options. Dr. Brass is a former employee of Merck and holds stock and/or stock options. Dr. Bacon has received consultancy fees from Gilead, Three Rivers Pharmaceuticals, Valeant, Vertex, and Human Genome Sciences; has grants/grants pending from Roche, Gilead, Bristol Myers Squibb, Three Rivers Pharmaceuticals, Valeant, Vertex, Human Genome Sciences, Wyeth, and Romark Laboratories; payment for lectures including service on speakers bureaus for Three Rivers Pharmaceuticals, Gilead, and Merck; and served on Data and Safety Monitoring Boards for Novartis, ISIS, Vertex, and Gilead. Dr. Esteban-Mur is a member of the speaker's bureau or is an advisor of Merck, Gilead, Novartis, Bristol-Myers Squibb, and GlaxoSmithKline.

* *Address correspondence to:* Jagpreet Chhatwal, Graduate School of Public Health, University of Pittsburgh, 130 De Soto Street, Crabtree Hall A647, Pittsburgh, PA 15261, USA.

E-mail: chhatwal@pitt.edu.

1098-3015/$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2013.07.006

The launch of two protease inhibitors (PIs)—boceprevir and telaprevir—in 2011 represents a major advance in the treatment of chronic HCV with significant improvements in SVR rates [6–9]. The Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol-2 (RESPOND-2) trial, an international, randomized, multicenter, double-blind study, demonstrated that boceprevir, when added to PR, leads to high SVR rates in patients with genotype 1 who failed prior treatment with PR therapy [8]. The SVR rates were significantly higher in the two boceprevir-containing regimens (59% and 66%) than in the control regimen of PR alone (21%, $P < 0.001$). RESPOND-2 did not include null responders. PROVIDE, a single-arm trial, however, evaluated the effectiveness of boceprevir in prior null responders and reported significantly higher SVR rates of 39% in comparison with a low historic rate of 16% using PR [10]. Similarly, the pivotal trial of telaprevir, retreatment of patients with telaprevir-based regimen to optimize outcomes (REALIZE), evaluated the addition of telaprevir to PR in patients with HCV genotype 1 infection who had no response or a partial response to previous therapy or who had a relapse after an initial response [7]. The SVR rates were significantly higher (33%–83%) with telaprevir-based regimens than in the control groups.

By substantially increasing the SVR rates, the use of PIs is expected to influence the course of the disease by reducing the incidence of liver-related complications and deaths. Because the treatment cost of PI-based triple therapy is substantially higher than that of PR therapy, it is not clear whether the PI-containing regimens provide sufficient value in patients who failed prior treatment with PR. The main objective of our study was to evaluate the cost-effectiveness of boceprevir-based regimens as studied in RESPOND-2 and PROVIDE in comparison with PR alone in previously treated patients with chronic HCV genotype 1 infection. In addition, we evaluated the cost-effectiveness of telaprevir in previously treated patients by using data from REALIZE.

Table 1 – Baseline patient characteristics from RESPOND-2.

Characteristics	N = 403
Sex, n (%)	
Male	268 (67)
Female	135 (33)
Age (y)	
Mean ± SD	52.7 ± 7.7
Range	26–74
Race, n (%)	
Black	49 (12)
Non-Black	354 (88)
Prior treatment experience, n (%)*	
Nonresponders	144 (36)
Relapsers	259 (64)
Baseline Metavir score, n (%)†	
F0—no fibrosis	18 (4)
F1—portal fibrosis without septa	200 (50)
F2—portal fibrosis with few septa	79 (20)
F3—numerous septa without cirrhosis	29 (7)
F4—cirrhosis	49 (12)
Missing‡	28 (7)

HCV, hepatitis C virus; RESPOND-2, Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol-2.

* Prior nonresponders had a decrease in plasma HCV-RNA levels of at least 2-$\log_{10}$ by week 12 of prior therapy but with detectable HCV-RNA levels throughout the course of therapy. Prior relapsers had undetectable HCV-RNA levels at end of prior therapy without subsequent attainment of a sustained virologic response.

† A central pathologist determined the fibrosis score. Twenty-eight patients had missing data.

‡ Patients with missing Metavir score were not included in the model.

Methods

We created a multicohort Markov model that simulated each cohort through the trial design of RESPOND-2, and projected health-related outcomes (costs and benefits) beyond the time period of the trial by using the natural history of progression of HCV disease. Each cohort was determined by the following risk factors or demographic characteristics: age (mean age), sex (male/female), and baseline fibrosis score (F0–F4). The patient characteristics were based on patients enrolled in the RESPOND-2 trial (Table 1). A total of 10 different patient profiles from RESPOND-2 defined the cohorts explored in our model.

Treatment Regimens Based on RESPOND-2 Study Design

The trial randomized 403 patients in a 1:2:2 ratio to one of three treatment groups (Fig. 1). The first group received PR for 48 weeks (abbreviated as PR48). The second group received response-guided-therapy (RGT), starting with 4 weeks of PR followed by boceprevir plus PR for 32 weeks (abbreviated as BOC/RGT). Those with undetectable HCV-RNA levels at weeks 8 and 12 completed therapy at week 36, whereas those with detectable HCV-RNA levels at week 8 (but undetectable at week 12) received PR for an additional 12 weeks. The third group received PR for 4 weeks followed by boceprevir plus PR for 44 weeks (abbreviated as BOC/PR48). In all three groups, patients who failed to achieve undetectable HCV-RNA levels at week 12 discontinued therapy and entered follow-up, regardless of their previous HCV-RNA level measurements. At the end of the treatment, patients were followed up to week 72.

Model Structure

We divided the model into two parts: the first part simulated the treatment strategies, and the second part modeled the natural history of the hepatitis C disease (Fig. 2). The treatment and follow-up period were modeled by using a weekly cycle to allow for early discontinuations, whereas the natural-history part used a cycle length of 1 year.

During the treatment phase, patients entered the model with chronic HCV disease and began antiviral drug therapy. At each cycle, a patient could discontinue treatment for medical or nonmedical reasons, fail to pass a futility rule, or continue treatment. Patients could develop anemia during treatment, which was managed by erythropoietin (EPO) or ribavirin dose reduction. At the end of treatment, patients who failed to pass a futility rule or had detectable HCV-RNA levels were considered treatment failures and returned to chronic HCV health states. Patients who had undetectable HCV-RNA levels at the end of treatment (i.e., end-of-treatment response) were followed for 24 weeks. After 24 weeks, if the patient still had undetectable HCV-RNA levels, the patient had achieved SVR; otherwise, he or she was considered to be a treatment relapse.

The second component of the model simulated the natural history of chronic HCV disease. The model was designed to be consistent with the current understanding of the biology of chronic HCV-related liver disease and its treatment and is similar to other published health economic models of HCV disease [11–14]. Our state-transition model consists of 14 health states (Fig. 2). States capturing the severity of chronic HCV infection are described by the degree of fibrosis by using the Metavir scoring system: no fibrosis (F0), portal fibrosis without septa (F1), portal

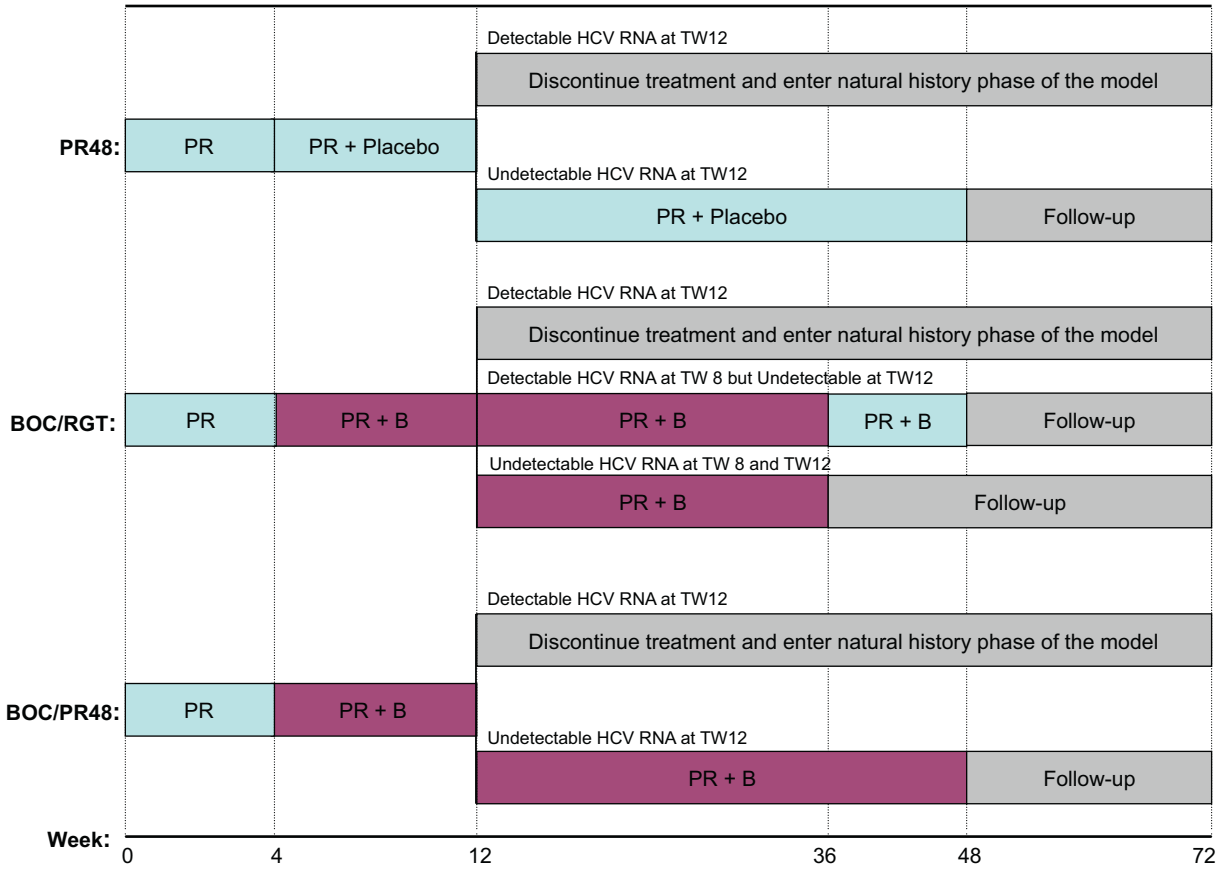

Fig. 1 – Strategies based on the RESPOND-2 trial for treatment-experienced patients. BOC/PR48, peginterferon–ribavirin-boceprevir regimen; BOC/RGT, response-guided therapy; HCV, hepatitis C virus; PR48, peginterferon-ribavirin regimen; RESPOND-2, Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol-2; TW, treatment week.

fibrosis with few septa (F2), numerous septa without fibrosis (F3), and cirrhosis (F4). In addition, the model includes states that define advanced liver diseases, liver transplant (LT), SVR (cirrhotic and noncirrhotic at baseline), and death. The model was developed by using Microsoft Excel (Microsoft Corp., Redmond, WA).

The progressive disease model assumed that a person with a given fibrosis score may progress to more severe stages of liver disease or may remain in that health state. In the absence of successful treatment, regression to less severe health states was not permitted. After a successful treatment, however, a person can achieve SVR, which was considered a cure for HCV in patients without cirrhosis. We assumed that a cured person who started treatment in health states F0 to F3 would not become symptomatic again. However, patients with cirrhosis continued to face some risk of liver disease (decompensated cirrhosis [DC] and HCC) even if they achieved SVR [15]. For this purpose, we stratified the SVR state by patient's baseline fibrosis stage before treatment ("SVR, F0–F3" and "SVR, F4").

Patients who return to chronic HCV health states can develop serious liver disease. Patients with compensated cirrhosis are at risk for developing DC and HCC. Although there are different modes of decompensation (i.e., ascites, variceal hemorrhage, and encephalopathy), we modeled them as one health state instead of different health states because these decompensation modes are not mutually exclusive. If a patient developed DC and/or HCC, then the patient could receive an LT. To account for different mortality rates of DC during the first year and subsequent years, the DC state was divided into two states: first year (DC1) and subsequent years (DC+). Similarly, the LT health state was divided into two—"Liver Transplant" and "Post-Liver Transplant." Patient in DC, HCC, and LT were subjected to excess mortality compared with the general population, whereas all other patients faced the same mortality risk as the general population.

Assumptions

We assumed that there is no progression of disease while patients are on treatment. This assumption will have only a minimal or no impact on results because HCV is a slow progressing disease that can take 20 to 30 years to reach cirrhosis from the no-fibrosis state whereas the treatment period lasts at most 48 weeks. In addition, only a fraction of patients in whom treatment will eventually fail continue beyond week 12. We did not model the possibility of remission from health states F0 and F1 because the likelihood of a chronically infected person spontaneously clearing HCV is very small [14]. As was done in many previous models, we assumed that all patients continue to progress when not treated. Some studies, however, suggest that a proportion of patients in the F0 state will not progress even if untreated [11,13]. This assumption biases the base-case analysis in favor of the use of triple therapy. The importance of this assumption was tested in the sensitivity analysis. Patients who received an LT were not explicitly modeled for the risk of reactivation and progression to liver disease. The post-LT state indirectly took into account the mortality, however, quality of life, and cost of reinfection after the LT. We also assumed no long-term benefits of treatment for patients who relapsed or did not respond. This assumption leads to the

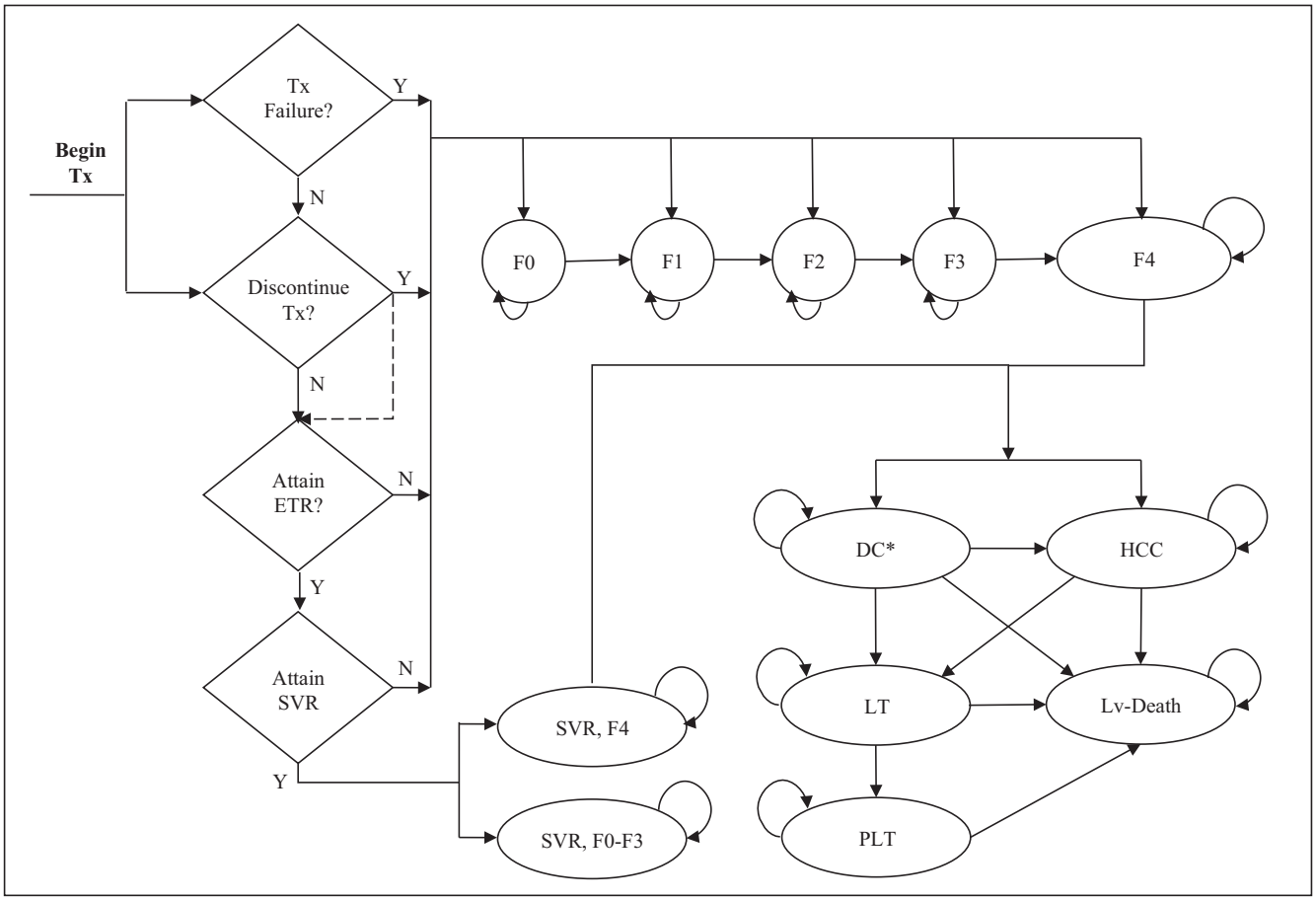

Fig. 2 – State-transition diagram for chronic hepatitis C and liver disease model. The model consists of two components: treatment and natural history. If patients discontinue treatment (Tx), or fail to achieve an end-of-treatment response (ETR) or a sustained virologic response (SVR), they enter the natural history component of the model, which consists of 14 health states. These include fibrosis states (F0–F4); decompensated cirrhosis (first year [DC1] and subsequent years [DC+]); hepatocellular carcinoma (HCC); liver transplant (first year [LT] and subsequent years [PLT]; liver-related death (Lv-Death); death from all other causes (not shown here); and SVR status states stratified by fibrosis stage ("SVR, F0–F3" and "SVR, F4"). N, no; Y, yes. *For clarity, two decompensated states—DC1 and DC+—are shown as one state, that is, DC.

underestimation of benefits of both dual and triple therapy. Because the proportion of patients who relapsed or did not respond was higher with dual therapy, this assumption also biases the analysis against the use of dual therapy. Our model included only the currently approved and available treatments, and did not include any treatment that would be available in the future.

Treatment-related inputs

We used RESPOND-2 data to estimate all treatment-related input parameters (Table 2). Specifically, we estimated efficacy rates, treatment-failure rates, probability and duration of anemia, and duration of EPO use for the management of anemia associated with each treatment strategy.

Epidemiological Inputs

The model required epidemiological inputs that describe the rate of HCV progression, the probability of receiving an LT, and both all-cause and liver-related mortality rates (Table 3). The progression rates determined the amount of time patients spent in each health state, the likelihood of developing serious complications associated with liver disease, and the probability of requiring an LT.

We used the progression rates of fibrosis stages from Thein et al. [16], a recent study that provides a systematic review and meta-analysis of published progression rates from 111 studies of individuals with chronic HCV infection. They provided stage-specific progression rates by fibrosis level. These estimates also adjust for biases attributable to study design and selection factors associated with the study population and clinical characteristics as shown in earlier studies [39].

We estimated the likelihood of cirrhosis advancing to DC from a pooled analysis of five studies [17–21] and cirrhosis advancing to HCC from a pooled analysis of nine studies [17–25]. The baseline likelihood of developing HCC from DC and the annual mortality associated with DC were estimated from a study by Planas et al. [26] that followed 200 patients with DC for a mean period of 32 months. The patients developing DC or HCC were eligible to receive an LT. The mortality associated with LT was estimated from a recently published study [31], which was not specific to patients with HCV; however, this was tested by sensitivity analysis. The age- and sex-specific all-cause mortality rates were taken from US life tables [40].

Probability of Receiving an LT

Most of the previously published US-based cost-effectiveness models used the probability of receiving an LT from DC estimated

Table 2 – Treatment-related outcomes of patients enrolled in RESPOND-2.

Treatment characteristics	PR48 (n = 80)	BOC/RGT (n = 162)	BOC/PR48 (n = 161)
Experienced anemia, n (%)	16 (20)*	70 (43)	75 (47)
EPO use, n (%)	17 (21)	66 (41)	74 (46)
Mean duration of anemia (d)	97.4	122.1	150.6
Mean duration of EPO use (d)	64.6	135.0	130.2
Discontinued before TW12, n/m (%)	5/80 (6)	13/162 (8)	4/161 (2.5)
Discontinued because of treatment failure at TW12, n/m (%)†	49/75 (65)	36/149 (24)	29/157 (18)
Discontinued after TW12, n/m (%)†	3/26 (12)	7/113 (6)	23/128 (18)
Assigned 36-wk therapy, n/m (%)†	NA	66/106 (62)	NA
Sustained virologic response (SVR), n (%)	17 (21)	95 (59)	107 (66)

BOC/PR48, peginterferon–ribavirin-boceprevir regimen; BOC/RGT, response-guided therapy; EPO, erythropoietin; NA, not applicable; PR48, peginterferon-ribavirin regimen; RESPOND-2, Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol-2; TW, therapy week.

* All patients receiving EPO were assumed as anemic by the model. Because more patients received EPO than who experienced anemia in PR48, the number of patients who experienced anemia in PR48 was assumed to be 17 in the model.

† Conditional on the proportion of subjects reaching this week in the trial (as needed by the model). The denominator was determined by the number of patients in the trial at the given week.

by using data from 1987 and 1997 [14]. The LT practice and the prevalence of DC in the US population, however, have changed since then. For example, according to the analysis of the Scientific Registry of Liver Transplant Recipients data, from 1999 to 2007, the number of recipients with HCV increased to a peak of 2,481 in 2006 and remained relatively unchanged afterwards [27]. Also, HCV-related DC became more prevalent after 1995 [28]. By using the approach of Bennett et al. [14] and most recent data, we estimated the annual probability of a patient with DC receiving an LT to be equal to 2.33% (i.e., 2,400/103,117). Our estimate is lower than that of Bennett et al. (3.1%) primarily because of a substantial increase in the prevalence of DC since then. Finally, we estimated the annual probability of a patient with HCC receiving an LT to be 4.0% from a study by Lang et al. [29].

Treatment Costs

The model was developed from the payer perspective. We estimated the baseline health-state–specific annual costs from a study by McAdam-Marx et al. [34] that conducted a retrospective, matched cohort study of 34,597 patients with HCV enrolled in a large managed care claims database. We subtracted pharmacy-related costs from HCV states without cirrhosis (F0–F3) and compensated cirrhosis (F4), which were primarily due to antiviral therapy. We also adjusted the inpatient hospitalization costs by using the national hospital cost-to-charge ratio of 0.329, which was estimated by taking the weighted average of statewide operating cost-to-charge ratio [41] and the number of hospital discharges in each state [42]. McAdam-Marx et al. provided only the combined cost associated with health states F0 to F3. To estimate the cost associated with each fibrosis stage, we used the proportion of cost spent in each health state—mild (F0, F1) to moderate (F2) to severe (F3) chronic HCV—from another study [35].

The total treatment costs for patients on antiviral therapy were based on the weekly drug costs and monitoring costs. We assumed the drug costs to be equal to the wholesale acquisition cost as listed by First DataBank [32]. The price of pegylated interferon alfa-2b was $587.51 per week. By using the price of the generic version of ribavirin equal to $8.83 per 200 mg capsule at a daily dose of 1000 mg and the mean patient body weight of approximately 80 kg, we estimated the weekly cost of ribavirin at $309.05. The weekly cost of boceprevir was $1100. The cost of treating anemia was estimated by using the percentage of patients who used EPO (at a weekly cost of $875) and the mean duration of EPO in the trial. We added a weekly monitoring cost of $64, which included physician visits, blood cell counts, liver function tests, and HCV quantitative polymerase chain reaction tests. We did not include any indirect costs (e.g., lost productivity) in the model. An annual discount rate of 3% was applied to future costs accrued.

Utility weights

All treatment and health-state–specific utility weights were estimated from a previously published study using the EuroQol five-dimensional questionnaire instrument [12,38], and adjusted to the US population norm [36]. Quality of life (QOL) of patients who achieved SVR was assumed to be equivalent to that of the general population [38]. Future QALYs were discounted at 3% per year.

Outcomes

Our model provided the average total costs and QALYs associated with each treatment strategy, and the incremental cost-effectiveness ratios (ICERs) per additional QALY of boceprevir-based regimens —BOC/PR48 and BOC/RGT—compared incrementally with PR. In addition, we projected the incidence of advanced liver-related complications (DC and HCC), LTs, and liver-related deaths (LRDs) with the three treatment strategies. A half-cycle correction was performed when calculating all outcomes. Finally, we performed one-way and probabilistic sensitivity analysis (PSA) to measure uncertainty in outcomes because of uncertainty in the efficacy, epidemiology, QOL, discount rates, and cost inputs.

Results

We cross-validated our model by comparing the natural history of HCV infection with previously published models. For this purpose, we projected the 20-year cumulative probability of developing cirrhosis in a 44-year-old untreated patient with F0 and F1 stage equal to 17.2% and 35.5%, respectively. Siebert et al. [12] projected the 20-year probability of cirrhosis in a 44-year-old patient with mild chronic HCV to be equal to 27%, and Bennett et al. [14] projected the corresponding probability in a 35-year-old patient with mild chronic HCV to be equal to 28%. Assuming 35% of the patients with mild HCV with the F0 stage and 65% with the F1 stage in 2010 [28], our model predicted the 20-year cirrhosis probability of 29.1% in a 44-year old patient, which is comparable to reported values. Salomon et al. [11] projected 30-year cumulative probability from F0 to cirrhosis and F2 to cirrhosis equal to 20% and 65%, respectively. The corresponding probabilities from our model were higher at 38.2% and 79%, respectively.

We also compared our results with a recently published multicenter follow-up study of patients with advanced fibrosis

Table 3 – Clinical, cost, and quality-of-life inputs, and SVR rates: baseline values, ranges, and parameters for distributions used in deterministic and probabilistic sensitivity analyses.

Input	Base case	Range	Distribution	Parameter 1*	Parameter 2†
Transition probabilities (annual)					
F0–F1 [16]	0.117	0.104–0.130	Beta	274.98	2,075.30
F1–F2 [16]	0.085	0.075–0.096	Beta	210.06	2,261.18
F2–F3 [16]	0.120	0.109–0.133	Beta	288.05	2,112.38
F3–F4 [16]	0.116	0.104–0.129	Beta	270.61	2,062.22
Cirrhosis to DC [17–21]	0.029	0.010–0.039	Beta	16.67	558.01
Cirrhosis to HCC [17–25]	0.028	0.010–0.079	Beta	22.97	791.67
SVR after cirrhosis to DC [15]	0.008	0.002–0.036	Beta	6,348.80	787,251.20
SVR after cirrhosis to HCC [15]	0.005	0.002–0.013	Beta	2,487.50	495,012.50
DC to HCC [26]	0.068	0.030–0.083	Beta	10.88	149.15
DC to transplantation [27,28]	0.023	0.010–0.062	Beta	1.31	55.44
DC (first year) to death from liver disease [26]	0.182	0.065–0.190	Beta	68.42	307.52
DC (subsequent year) to death from liver disease [26]	0.112	0.065–0.190	Beta	28.13	223.02
HCC to transplantation [29,30]	0.040	0.000–0.140	Beta	3.88	93.09
HCC to death from liver disease [18]	0.427	0.330–0.860	Beta	263.82	354.02
Liver transplantation (first year) to death from liver disease [31]	0.116	0.060–0.420	Beta	30.04	228.91
Following liver transplantation to death from liver disease [31]	0.044	0.024–0.110	Beta	4.67	101.55
Drug therapy–related costs (weekly)					
Peginterferon alfa-2b [32]	588				
Ribavirin [32]	309				
Boceprevir [32]	1,100				
Erythropoietin (40,000 IU/mL) [32]	875				
Monitoring costs [33]	64				
Health state costs (annual)					
F0, F1 [34,35]	678	±25%	Gamma	61.47	11.03
F2 [34,35]	687	±25%	Gamma	61.47	11.17
F3 [34,35]	1,394	±25%	Gamma	61.47	22.67
Compensated cirrhosis [34]	1,626	±25%	Gamma	61.47	26.46
DC [34]	18,064	±25%	Gamma	61.47	293.89
HCC [34]	33,218	±25%	Gamma	61.47	540.44
Liver transplant (first year) [34]	95,971	±25%	Gamma	61.47	1,561.38
Following liver transplant [34]	25,208	±25%	Gamma	61.47	410.11
Health state quality-of-life weights					
US population norms, men [36]					
20–29 y	0.928	0.922–0.934	Beta	6,616.65	513.36
30–39 y	0.918	0.912–0.925	Beta	7,374.10	658.69
40–49 y	0.887	0.880–0.894	Beta	6,970.14	887.97
50–59 y	0.861	0.853–0.870	Beta	6,185.19	998.54
60–69 y	0.840	0.827–0.852	Beta	2,566.28	488.82
70–79 y	0.802	0.788–0.816	Beta	2,496.15	616.26
80–89 y	0.782	0.757–0.807	Beta	819.41	228.43
US population norms, women [36]					
20–29 y	0.913	0.905–0.920	Beta	4,353.04	414.80
30–39 y	0.893	0.886–0.900	Beta	6,689.64	801.56
40–49 y	0.863	0.855–0.871	Beta	6,124.55	972.26
50–59 y	0.837	0.829–0.846	Beta	6,854.42	1,334.85
60–69 y	0.811	0.800–0.822	Beta	3,946.67	919.75
70–79 y	0.771	0.758–0.784	Beta	3,094.35	919.07
80–89 y	0.724	0.701–0.747	Beta	1,050.61	400.51
Drug therapy–related multiplier [12]	0.90	0.84–0.96	Beta	86.44	9.60
Anemia multiplier [37]	0.83	0.75–0.97	Beta	70.30	14.40
F0, F1 [38]	0.93	0.84–1.00	Beta	47.47	3.57
F2, F3 [38]	0.93	0.84–1.00	Beta	47.47	3.57
Compensated cirrhosis [38]	0.90	0.81–1.00	Beta	31.12	3.46
DC [38]	0.80	0.57–1.00	Beta	12.29	3.07
HCC [38]	0.79	0.54–1.00	Beta	11.42	3.03
First-year, following liver transplant [38]	0.84	0.77–0.93	Beta	53.54	10.20
Post-SVR	1.00	0.92–1.0	Beta	6,368.04	15.96

Table 3 – *continued*

Input	Base case	Range	Distribution	Parameter 1*	Parameter 2†
SVR rates					
PR48 [8]	0.21	0.13–0.30	Beta	19.56	72.50
BOC/RGT [8]	0.59	0.51–0.66	Beta	92.87	65.50
BOC/PR48 [8]	0.66	0.59–0.74	Beta	108.65	54.83

BOC/PR48, peginterferon–ribavirin-boceprevir regimen; BOC/RGT, response-guided therapy; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; PR48, peginterferon-ribavirin regimen; SVR, sustained virologic response.
* Parameter 1 corresponds to the α parameter for beta distribution and the k (shape) parameter for gamma distribution.
† Parameter 2 corresponds to the β parameter for beta distribution and the θ (scale) parameter for gamma distribution.

by van der Meer et al. [43]. In patients who failed to achieve SVR, the study reported the 10-year cumulative incidence rates of DC, HCC, and combined LRD and LT equal to 29.9% (CI 24.3%–35.5%), 21.8% (95% CI 16.6%–27.0%), and 27.4% (95% CI 22.0%–32.8%), respectively. The corresponding values predicted by our model were 17.0%, 18.7%, and 23.7%, respectively. The predicted incidence of HCC and LRD plus LT in this group was within the reported CIs; however, the incidence of DC was lower than the reported values. In patients who achieved SVR, the study reported the 10-year cumulative incidence rates of DC, HCC, and combined LRD and LT equal to 2.1% (95% CI 0%–4.5%), 5.1% (95% CI 1.3%–8.9%), and 1.9% (95% CI 0%–4.1%), respectively. The corresponding values predicted by our model were 5.2%, 3.9%, and 5.6%, respectively. The predicted incidence of HCC in this group was within the reported CIs; however, the incidence of DC and LRD plus LT was higher than the reported values.

Base-Case Analysis

Treatment with PR therapy would result in a 16.0% likelihood of DC compared with 9.4% (relative reduction of 41.1%) with BOC/RGT and 8.1% (relative reduction of 49.4%) with BOC/PR48 (Fig. 3). Similarly, the likelihood of HCC, LT, and LRD was projected to reduce by 41.1% to 52.0% with boceprevir-based regimens in comparison with PR48. The total projected life-years associated with PR48, BOC/RGT, and BOC/PR48 were 24.74, 26.07, and 26.34, respectively, and the corresponding discounted QALYs were 12.79, 13.64, and 13.80, respectively (Table 4). The total expected discounted lifetime costs of PR48, BOC/RGT, and BOC/PR48 were $53,500, $79,000, and $94,500, respectively. The average boceprevir cost account for 33% and 39% of total HCV-associated cost in BOC/RGT and BOC/PR48, respectively (Table 4). The ICER of BOC/RGT in comparison with that of PR48 was $30,200 per QALY, and the ICER of BOC/PR48 in comparison with that of BOC/RGT was $91,500 per QALY.

Sensitivity Analysis

We performed one-way sensitivity analysis on efficacy, transition probabilities, QOL weights, discount rates, and treatment-related costs, and identified the top 25 variables that had the biggest impact on ICERs by plotting the tornado diagrams (Figs. 4 and 5). We found that ICERs were most sensitive to the SVR rates, discount rate, probability of DC or HCC in patients with cirrhosis, probability of DC after achieving SVR, and QOL weights associated with fibrosis stages F0 to F4.

We also analyzed a scenario in which 24% of the patients with the F0 stage will not progress even without treatment, and found similar results as with the base-case analysis. Next, we performed sensitivity analysis by including the hazard ratio for sex-, race-, and age-specific mortality (white male: 2.56; white female: 1.90; black male: 2.75; and black female: 2.48) from nonliver causes in patients with chronic HCV [13]. By using the proportion of blacks and whites from RESPOND-2, we estimated the weighted hazard ratio for males as 2.58 and females as 1.97. We linearly decreased the hazard ratio from age 70 years onwards to 1.0 by age 100 years to avoid the overestimation of mortality in older patients. The cost of PR48, BOC/RGT, and BOC/PR48 went down to $50,000, $74,600, and $90,568 respectively. The corresponding QALYs went down to 10.63, 11.22, and 11.34, respectively. The ICER of BOC/RGT in comparison with that of PR48 was $48,900 per QALY, and the ICER of BOC/PR48 in comparison with that of BOC/RGT was $138,100 per QALY.

Next, we performed PSA on the parameters defined in Table 3. By using 10,000 Mote Carlo simulations, the total mean QALYs associated with PR48, BOC/RGT, and BOC/PR48 were found to be 13.48, 14.48, and 14.61, respectively, and the corresponding total expected cost was $55,785, $80,398, and $95,570, respectively. At a willingness-to-pay (WTP) threshold of $50,000, the probabilities of BOC/RGT and BOC/PR48 being the preferred option were 0.74 and 0.25, respectively (Fig. 6). At a WTP threshold of $100,000, the corresponding probabilities were 0.41 and 0.59.

Subgroup Analysis: Prior Treatment Response

Efficacy of re-treatment in patients who failed to achieve SVR earlier depends on the patients' response to prior treatment [8]; hence, the cost-effectiveness of re-treatment may vary by patients' prior treatment response. We performed cost-effectiveness analysis in the following three subgroups: 1) Prior relapsers, that is, patients with undetectable HCV-RNA levels at the end of treatment but failed to achieve SVR; 2) Partial responders, that is, patients whose HCV-RNA levels decreased by at least 2 $\log_{10}$ at week 12 but remained detectable during the therapy period); and 3) Null responders, that is, patients whose HCV-RNA levels decreased by less than 2 $\log_{10}$ at week 12.

The treatment regimens and efficacy data of prior relapsers and partial responders were based on the RESPOND-2 study (see Table S1 of the Appendix in Supplemental Materials found at http://dx.doi.org/2010.1016/j.jval.2013.07.006). Because null responders were not included in RESPOND-2, we used data from an ongoing PROVIDE study to evaluate the cost-effectiveness in this subgroup [10]. For the comparator strategy of treatment with peginterferon-ribavirin, we estimated model parameters of null responders from an earlier study [44]. The treatment regimen of null responders was defined as follow: initiate with a lead-in period with PR alone for 4 weeks, followed by BOC + PR for 44 weeks (see Fig. S2 in Supplemental Materials found at http://dx.doi.org/2010.1016/j.jval.2013.07.006). In all patients, the treatment was stopped if they either had HCV-RNA greater than or equal to 100 IU/mL at treatment week 12, or detectable at treatment week 24. Table S2 in Supplemental Materials found at http://dx.doi.org/2010.1016/j.jval.2013.07.006 summarizes treatment-related data of null responders used in our model.

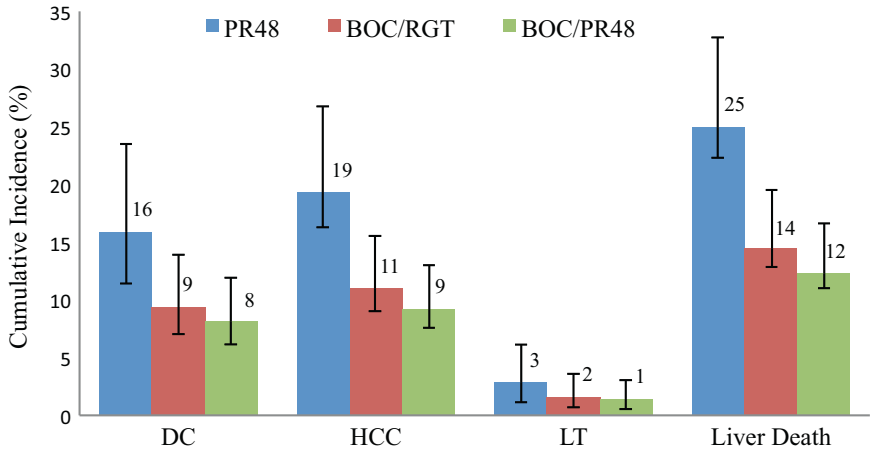

Fig. 3 – Cumulative incidence of liver-related complications with PR48, BOC/RGT, and BOC/PR48 treatment strategies. BOC/PR48, peginterferon–ribavirin-boceprevir regimen; BOC/RGT, response-guided therapy; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; PR48, peginterferon-ribavirin regimen. Error bars were estimated by using 10,000 Monte Carlo simulation runs.

In prior relapsers, the ICER of BOC/RGT in comparison with PR48 was $29,000, and the ICER of BOC/PR48 compared with BOC/RGT was $134,300 (Table 5). In partial responders, the corresponding ICERs were $33,600 and $58,200 per additional QALY. Finally, in null responders, the ICER of boceprevir-based regimen in comparison with PR48 was $33,300 per additional QALY. The cost-effectiveness results in the three subgroups were comparable, and the boceprevir-based triple therapy was cost-effective (using a WTP threshold of $100,000) irrespective of prior treatment response to therapy. Because RESPOND-2 was neither designed nor powered to detect differences in outcomes by treatment history, caution should be taken in interpreting the cost-effectiveness of boceprevir in these subgroups.

Subgroup Analysis: IL-28B Genotype

Response to interferon-based therapies is known to depend on interleukin (IL)-28B polymorphism [45]. Data from the RESPOND-2 study showed that single nucleotide polymorphism at IL-28B rs12979860 is strongly associated with response to triple therapy [46], with the CC genotype having a more favorable treatment response than non-CC genotypes. Therefore, we evaluated the cost-effectiveness of triple therapy by patient's IL-28B genotype. We used efficacy as the main input of our subgroup analysis by IL-28B genotypes. It should be noted that the RESPOND-2 trial was neither designed nor powered to assess the impact of the IL-28B genotype on the SVR. Also, approximately one third of the patients in RESPOND-2 did not consent to genomic testing. For these reasons, we did not include race (and other treatment-specific parameters) into our analysis by the IL-28B genotype. Because of the relatively low cost, we also did not include the cost of a one-time genotype IL-28B test. Table S3 in Supplemental Materials found at http://dx.doi.org/2010.1016/j.jval.2013.07.006 summarizes the data available from RESPOND-2 that was used in our model. Because discontinuation rates and treatment failure rates were not available by the IL-28B genotype, we used the corresponding rates as estimated in base-case analysis.

In IL-28B CC patients, the ICER of BOC/RGT in comparison with PR48 was $35,400 per additional quality-adjusted life-year

Table 4 – Life expectancy, breakdown of total discounted expected costs and QALYs, and the ICER associated with each treatment strategy.

Category	Cost ($)			QALYs*		
	PR48	BOC/RGT	BOC/PR48	PR48	BOC/RGT	BOC/PR48
Life expectancy	NA	NA	NA	24.74	26.07	26.34
Drug†	19,948	52,787	69,776	NA	NA	NA
Anemia	1,716	6,875	7,480	–0.01	–0.02	–0.02
Monitoring	1,423	1,929	2,376	NA	NA	NA
SVR	0	0	0	2.90	7.99	9.06
F0–F3	7954	4560	3843	7.06	4.1	3.47
F4	5,376	2,928	2,428	2.41	1.31	1.09
DC	5,933	3,560	3,078	0.21	0.13	0.11
HCC	7,096	4,070	3,453	0.14	0.08	0.07
Liver transplant	4,028	2,376	2,041	0.08	0.05	0.04
Total	53,474	79,085	94,475	12.79	13.64	13.8
ICER ($/QALY)				–	30,241	91,506

BOC/PR48, peginterferon–ribavirin-boceprevir regimen; BOC/RGT, response-guided therapy; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; PR48, peginterferon-ribavirin regimen; QALYs, quality-adjusted life-years.

* QALYs were rounded to two decimal places for reporting in the table, but ICERs were estimated by using exact QALYs from the model.

† Drug cost includes dual-therapy cost for PR48 and triple-therapy cost for BOC/RGT and BOC/PR48.

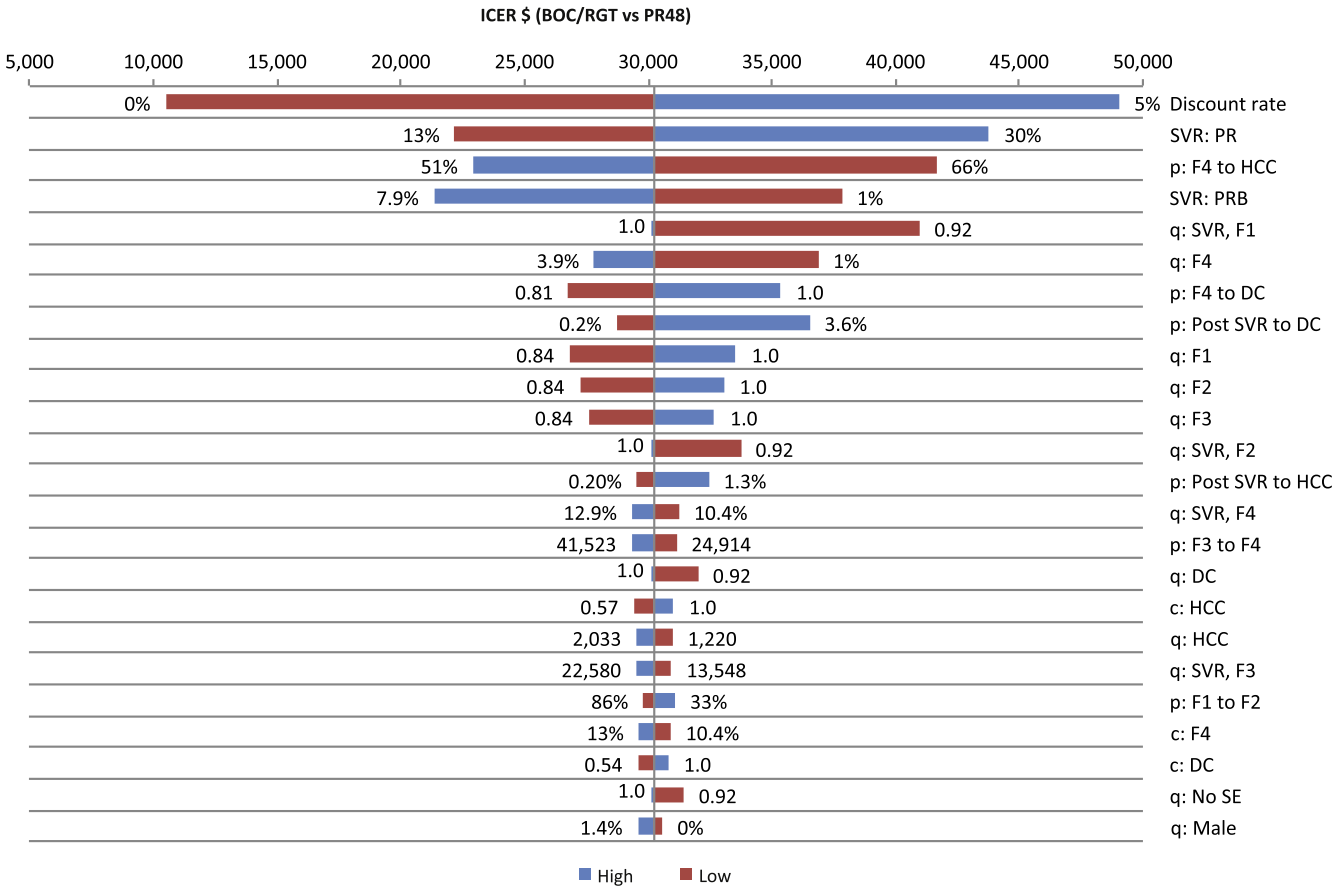

Fig. 4 – Tornado diagram showing 25 most sensitive parameters in BOC/RGT. BOC/RGT, response-guided therapy; c, cost; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; p, transition probability; PR48, peginterferon-ribavirin regimen; q, quality-of-life weight; SVR, sustained virologic response.

(QALY), and BOC/PR48 was dominated (Table 5). In IL-28B CT patients, the ICERs of BOC/RGT and BOC/PR48 were $24,800 and $51,400 per additional QALY, respectively. Finally, in IL-28B TT patients, BOC/RGT was ruled out using extended or weak dominance principle (because BOC/RGT had lower QALYs but higher ICER than did BOC/PR48), resulting in BOC/PR48's ICER of $97,000 per additional QALY in comparison with PR48. By using a WTP threshold of $100,000, boceprevir-based RGT was found to be cost-effective in patients with genotype CC and genotype CT. BOC/RGT, however, was weakly dominated in patients with genotype TT; instead, the 48-week fixed-treatment arm was cost-effective in patients with genotype TT. RESPOND-2 was neither designed nor powered to detect differences in outcomes by the IL-28B genotype; therefore, caution should be taken in interpreting the cost-effectiveness of boceprevir in these subgroups.

Scenario Analysis: Food and Drug Administration–Approved Regimens

The Food and Drug Administration (FDA) recommendations and the American Association for the Study of Liver Diseases treatment guidelines for the use of boceprevir are different than those studied in RESPOND-2; therefore, our model also simulated the recommended treatment design [47]. The FDA recommends BOC/RGT in treatment-experienced patients without cirrhosis who are prior relapsers or partial responders, and fixed-duration therapy of 48 weeks in null responders and patients with cirrhosis (see Figs. S1 and S2 in Supplemental Materials found at http://dx.doi.org/2010.1016/j.jval.2013.07.006). In addition, the boceprevir label recommended a different stopping rule than that applied in the RESPOND-2 trial. We performed post hoc analysis to estimate label-related model parameters (details are provided in Table S4 in Supplemental Materials found at http://dx.doi.org/2010.1016/j.jval.2013.07.006).

In patients without cirrhosis, the ICER of PR + BOC in comparison with that of PR was $35,300/QALY (Table 5). In patients with cirrhosis, the ICER of PR + BOC in comparison with that of PR was $10,100 per additional QALY. In comparison with the trial-based analysis, the label-based analysis shows a more favorable cost-effectiveness of treatment with triple therapy. In addition, the treatment with triple therapy provides more benefits per dollar spent in patients with cirrhosis than in patients without cirrhosis.

Scenario Analysis: Management of Anemia with Ribavirin Dose Reduction

Although EPO was used to manage anemia in RESPOND-2, a recent study showed that SVR rates in patients managed with ribavirin dose reduction alone were comparable to those in patients managed with EPO [48]. Our base-case analysis assumed management of anemia with EPO use as observed in the trial; however, we also analyzed a scenario in which all anemic patients would be managed with ribavirin dose reduction only. For this scenario, the ICER of BOC/RGT in comparison with that of PR48 and the ICER of BOC/PR48 in comparison with that of BOC/RGT went down to $24,100 and $87,900, respectively (Table 5).

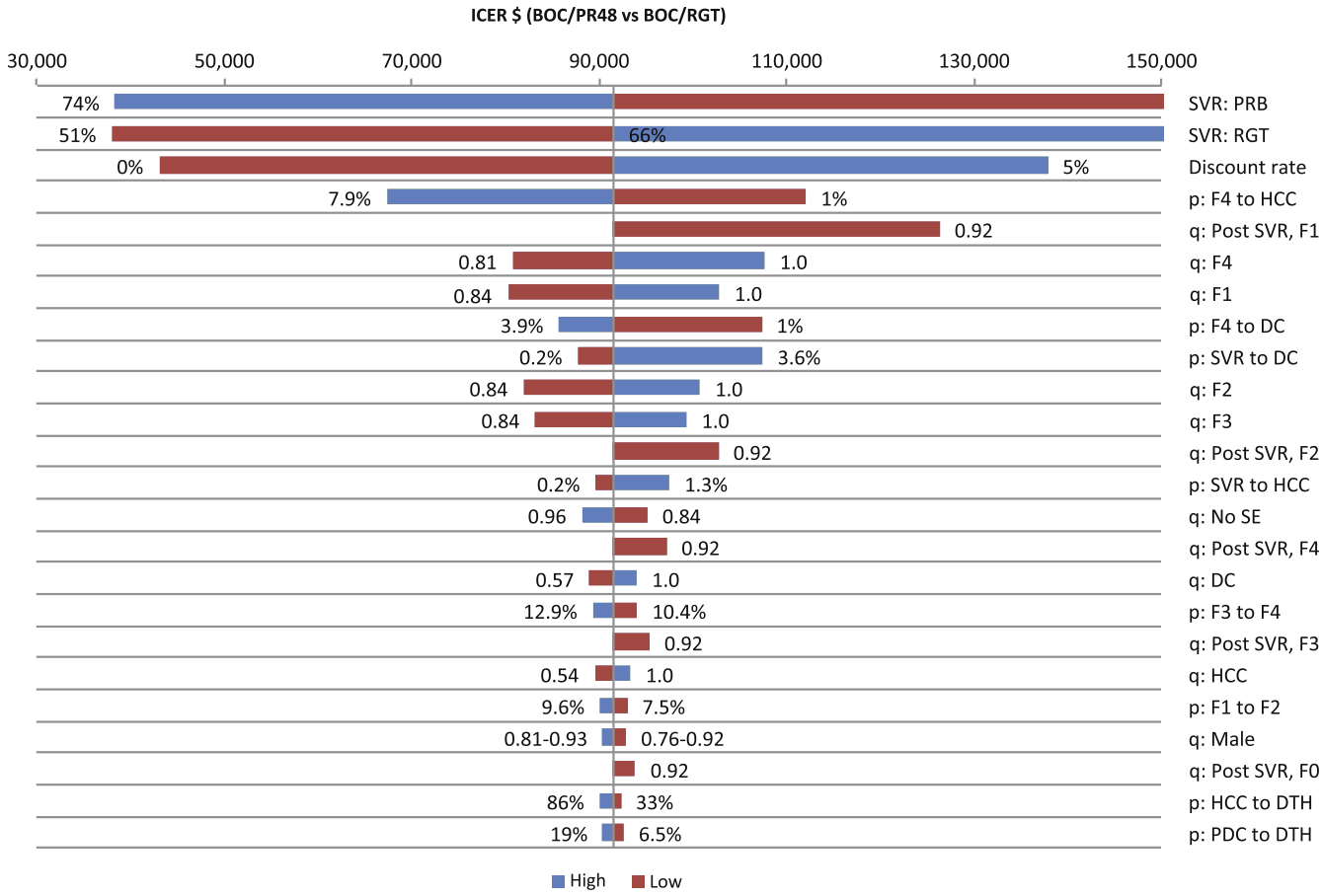

Fig. 5 – Tornado diagram showing 25 most sensitive parameters in BOC/PR48. BOC/PR48, peginterferon–ribavirin-boceprevir regimen; BOC/RGT, response-guided therapy; c, cost; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; p, transition probability; q, quality-of-life weight; SVR, sustained virologic response.

Telaprevir-Based Analysis

In addition to boceprevir, FDA approved another protease inhibitor, telaprevir, for chronic hepatitis C treatment in previously treated patients [7]. Because no head-to-head trial compares the effectiveness of telaprevir with boceprevir, and the baseline patient characteristics, adverse event profiles, and futility rules of RESPOND-2 and REALIZE were different, direct comparison of the cost-effectiveness of the two drugs was not feasible. Therefore, we evaluated only the cost-effectiveness of telaprevir in previously treated patients in comparison with peginterferon-ribavirin using data from the REALIZE study [7].

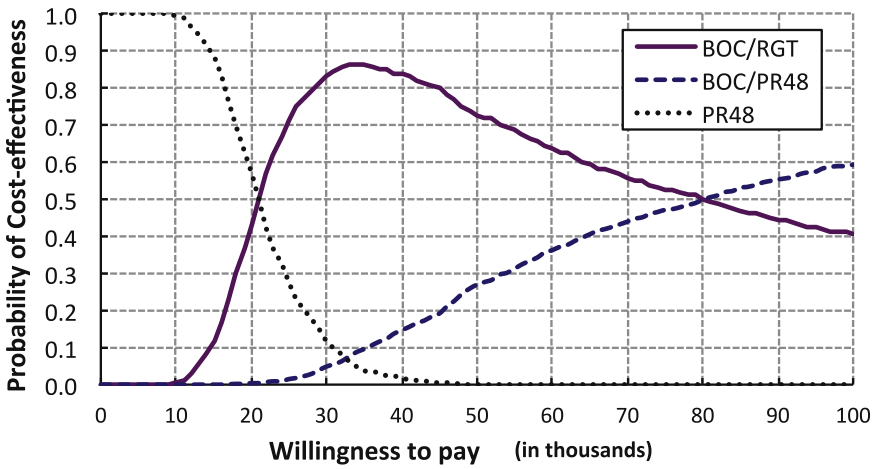

Fig. 6 – Cost-effectiveness acceptability curve. BOC/PR48, peginterferon–ribavirin-boceprevir regimen; BOC/RGT, response-guided therapy; PR48, peginterferon-ribavirin regimen.

Table 5 – Subgroup and scenario analysis of total discounted expected costs and QALYs, and the ICER associated with each treatment strategy.

Treatment strategy	Cost ($)	QALYs	ICER ($/QALY)	Prob. of CE at $50K	Prob. of CE at $100K
Subgroup analysis by prior treatment response					
Prior relapser					
PR48	54,413	12.98	–	0.022	0
BOC/RGT	80,208	13.87	29,017	0.830	0.556
BOC/PR48	97,225	13.99	134,363	0.148	0.444
Partial responder					
PR48	51,897	12.46	–	0.062	0
BOC/RGT	77,716	13.23	33,613	0.510	0.313
BOC/PR48	91,846	13.47	58.177	0.428	0.687
Null responder					
PR48	51,149	12.30	–	0.059	0.001
BOC/PR48	80,487	13.18	33,255	0.941	0.999
Subgroup analysis by IL-28B rs12979860 genotype					
IL-28B genotype CC					
PR48	45,225	13.35	–	0.259	0.080
BOC/RGT	71,372	14.08	35,444	0.672	0.717
BOC/PR48	90,893	14.05	Dominated*	0.069	0.203
IL-28B genotype CT					
PR48	54,803	12.70	–	0.005	0
BOC/RGT	79,468	13.69	24,832	0.539	0.291
BOC/PR48	92,399	13.94	51,393	0.456	0.709
IL-28B genotype TT					
PR48	43,951	13.43		0.680	0.401
BOC/RGT	82,746	13.54	Dominated†	0.138	0.152
BOC/PR48	92,566	13.93	97,077	0.182	0.447
Scenario analysis: FDA-approved regimens					
All previously treated					
PR48-FDA	55,603	12.73	–	0	0
BOC/PR-FDA	84,011	13.83	25,747	1	1
Patients without cirrhosis (Metavir F0–F3)					
PR48-FDA	51,125	13.26	–	0.065	0
BOC/PR-FDA	78,947	14.05	35,285	0.935	1
Patients with cirrhosis (Metavir F4)					
PR48-FDA	85,394	9.18	–	0	0
BOC/PR-FDA	117,701	12.37	10,102	1	1
Scenario analysis: management of anemia with ribavirin dose reduction					
PR48	51,759	12.79	–	0.001	0
BOC/RGT	72,209	13.64	24,149	0.729	0.406
BOC/PR48	86,995	13.80	87,906	0.270	0.594
Scenario analysis: telaprevir vs. peginterferon-ribavirin					
All previously treated					
REALIZE-PR48	71,299	12.32	–	0	0
TEL12PR48	108,795	13.85	24,431	1	1
Prior relapser					
REALIZE-PR48	76,040	12.55	–	0	0
TEL12PR48	103,595	14.47	14,397	1	1
Partial responder					
REALIZE-PR48	63,417	12.23	–	0	0.001
TEL12PR48	107,135	13.67	30,322	1	0.999
Null responder					
REALIZE-PR48	67,516	11.94	–	0.942	0
TEL12PR48	120,214	12.73	66,779	0.058	1

BOC/PR48 peginterferon–ribavirin-boceprevir regimen as in the RESPOND-2 trial; BOC/PR-FDA, boceprevir-based triple therapy as in the FDA-approved label; BOC/RGT, response-guided therapy as in the RESPOND-2 trial; CE, cost-effectiveness; FDA, Food and Drug Administration; ICER, incremental cost-effectiveness ratio; Prob., probability, PR48, peginterferon-ribavirin regimen as in the RESPOND-2 trial; PR48-FDA, peginterferon-ribavirin regimen as in the FDA-approved label; QALY, quality-adjusted life-year; REALIZE, retreatment of patients with telaprevir-based regimen to optimize outcomes; REALIZE-PR48, peginterferon-ribavirin regimen as in the REALIZE trial; RESPOND-2, Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol-2; TEL12PR48, telaprevir-based triple therapy as in the REALIZE trial.

* BOC/PR48 was dominated because it had lower QALYs but higher cost than did BOC/RGT.

† BOC/RGT was weakly dominated because it had lower QALYs but higher ICER than did BOC/PR48.

As in the case of boceprevir, the model was divided into two parts: the first part simulated the treatment strategies, and the second part modeled the natural history of the hepatitis C disease. We simulated treatment with peginterferon plus ribavirin for 48 weeks (REALIZE-PR48) and the FDA-approved treatment arm using telaprevir for 12 weeks and peginterferon plus ribavirin for a total of 48 weeks without any lead-in (T12PR48). The treatment was discontinued if patients had less than a 2 $\log_{10}$ decrease in HCV-RNA levels at week 12 (futility rule). All treatment-related parameters are summarized in Table S5 of the Appendix in Supplemental Materials found at http://dx.doi.org/2010.1016/j.jval.2013.07.006. Any patient who either failed to achieve SVR or a patient with cirrhosis (even if he or she achieved SVR) continued to the natural history part of the model.

By using the telaprevir price of $4,400 per week, the ICER of T12PR48 in comparison with that of REALIZE-PR48 was found to be $24,400/QALY (Table 5). The cost-effectiveness of telaprevir compared with that of PR was more favorable in prior relapsers (ICER = $14,400/QALY) and partial responders (ICER = $30,300/QALY) than in null responders (ICER = $66,800/QALY).

Discussion

A significant increase in SVR rates was observed in patients treated with boceprevir-based therapies over PR therapy alone in RESPOND-2 and PROVIDE [8]. It is not clear, however, whether the boceprevir-containing regimens provide sufficient value in previously treated patients given the high cost of triple therapy. We developed a Markov-cohort model to project the lifetime clinical burden of HCV, total cost, and cost-effectiveness of boceprevir-based regimens studied in RESPOND-2 and PROVIDE. We also estimated the cost-effectiveness of boceprevir regimens as per FDA recommendations and American Association for the Study of Liver Diseases guidelines, and telaprevir-based regimens as studied in the REALIZE trial.

Boceprevir-based regimens were projected to reduce the incidence of liver-related complications (DC and HCC), mortality, and LTs by 43% to 53% in comparison with treatment with PR alone. At a price of $1,100 per week, only RGT was cost-effective at a WTP threshold of $50,000/QALY , whereas both RGT and fixed-duration therapy for 48 weeks were cost-effective at a WTP threshold of $100,000/QALY . In addition, boceprevir-based regimens as approved by the FDA were also cost-effective in previously treated patients with HCV genotype 1 but with and without cirrhosis.

We performed subgroup analysis by prior treatment response and patient's IL-28B genotype. Our results show that both boceprevir-based therapies were cost-effective irrespective of patient's prior response to treatment, that is, prior relapsers, partial responders, and null responders. Second, the boceprevir-based RGT was found to be cost-effective in patients with the IL-28B genotype CC and CT at a WTP threshold of $50,000, whereas in patients with the IL-28B genotype TT, boceprevir-based RGT therapy was weakly dominated by fixed-duration boceprevir-based therapy, which was cost-effective only at a WTP threshold of $100,000. Because RESPOND-2 was neither powered nor designed to detect differences by subgroups, caution should be taken in interpreting the cost-effectiveness results in these subgroups.

We also evaluated the cost-effectiveness of telaprevir-based triple therapy in comparison with that of peginterferon-ribavirin using REALIZE trial results. At a price of $4,400 per week, telaprevir-based therapy was cost-effective in patients with genotype 1 who are prior relapsers and partial responders (using the WTP threshold of $50,000). In null responders, however, telaprevir-based therapy was cost-effective only at the WTP threshold of $100,000. We did not perform a direct comparison of cost-effectiveness of telaprevir with boceprevir because no head-to-head trial compares the effectiveness of these two drugs.

Our model was extensively validated against a recently published clinical study as well as with other modeling studies. The predicted progression to advanced HCV diseases in patients who failed to achieve SVR was lower and in patients who achieved SVR was higher in comparison to those reported in van der Meer et al. [43]. This trend may have resulted in an overestimation of ICERs of boceprevir-based regimens. In comparison with the modeling study of Salomon et al. [11], our model projected faster progression of fibrosis in untreated patients. The difference could be attributed to the exclusion of nonprogressing patients in stage F0, different natural history parameters, and assumption of no higher all-cause mortality in the base model. However, our model's fibrosis progression rates were similar to those reported in Bennett et al. [14] and Siebert et al. [12].

A recently published study evaluated the cost-effectiveness of boceprevir and telaprevir in patients who failed prior treatment in Europe and found very similar results [49]. To our knowledge, no previous study has evaluated the cost-effectiveness of treatment with PIs in patients who failed prior treatment in the United States. Several studies have evaluated the cost-effectiveness of PIs in treatment-naive patients [13,50,51]. We also made several updates in the model structure and inputs, in comparison with previously published models on hepatitis C. First, our model included two components—treatment phase and natural history phase—and included early discontinuations and management of anemia. Second, we estimated the probability of receiving an LT that takes into account the changes in the practice over the last two decades. Third, we estimated the probability of HCC after cirrhosis or DC by using a pooled analysis of several studies. Fourth, unlike most previous models, we allowed for a progression of disease in patients with cirrhosis even after they attained SVR. Finally, we estimated health-state–related costs by using a recent data and appropriate cohort of patients with hepatitis C.

Sensitivity analysis showed that the ICERs were most sensitive to the joint discount rates for costs and QALYs. We also found that ICERs were sensitive to the probability of development of HCC or DC in patients with cirrhosis, and QOL weights associated with fibrosis stages. This underscores a need for a better understanding of the natural history of end-stage liver diseases and QOL of patients with HCV. When we considered a higher mortality due to nonliver causes in patients with HCV, only RGT was cost-effective in comparison with PR-based therapy at a WTP threshold of $100,000. Finally, PSA showed that boceprevir-based regimens were cost-effective with a very high probability at commonly used WTP thresholds. In general, our conclusions were robust to a wide range of input parameters.

Our study has several limitations. First, we did not model the possibility of reinfection after a patient in stage F3 achieved SVR and assumed that DC and HCC are mutually exclusive, whereas this may not be the case in real life. This may have underestimated the ICERs of boceprevir-based therapies. Second, our model cannot be applied to special populations such as HIV-HCV or HBV-HCV coinfected patients because RESPOND-2 enrolled patients without such coinfections. Third, we assumed that there is no progression of disease while patients are on treatment, which may have some impact (albeit small) on our results. Fourth, our model was based on trial data whereas treatment-related parameters such as SVR rates, discontinuations, and treatment-completion rates may be different in practice, and influence the cost-effectiveness of boceprevir-based regimens. Fifth, we did not use higher all-cause mortality in patients with HCV in our base case, which resulted in an underestimation of ICERs of boceprevir-based therapies. Sixth, our PSA assumed

independence of all variables; however, costs and QOL weights are correlated, which may potentially bias our results. Finally, though IL-28B-guided therapy may be valuable in treatment-experienced patients, considering the above factors and lack of reliable data on IL-28B in treatment-experienced patients, we did not perform IL-28B genotype–guided analysis.

In summary, PIs were projected to substantially reduce the burden of liver-related complications such as DC, HCC, liver-related mortality, and LTs in previously treated patients with HCV genotype 1. In addition, first-generation PIs were projected to be cost-effective in comparison with treatment with peginterferon and ribavirin in previously treated patients at a WTP threshold of $100,000 [44].

Acknowledgments

We thank Drs. John R. Cook (Merck) and Erik Dasbach (Merck) for providing programming support, helpful discussions, and reviewing the model; Jane Liao (Merck) for providing programming support to determine the model inputs; and Dr. Heather L. Sings (Merck) for medical writing support.

Source of financial support: Dr. Chhatwal's effort was in parts supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number KL2TR000146. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This study was sponsored in part by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2013.07.006 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES

[1] Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335–74.
[2] Hepatitis C Fact Sheet. Geneva: World Health Organization. Available from: http://www.who.int/mediacentre/factsheets/fs164/en. [Accessed December 8, 2012].
[3] Ly KN, Xing J, Klevens RM, et al. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med 2012;156:271–8.
[4] Rustgi VK. The epidemiology of hepatitis C infection in the United States. J Gastroenterol 2007;42:513–21.
[5] Camm C, Cabibbo G, Bronte F, et al. Retreatment with pegylated interferon plus ribavirin of chronic hepatitis C non-responders to interferon plus ribavirin: a meta-analysis. J Hepatol 2009;51:675–81.
[6] Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405–16.
[7] Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011;364:2417–28.
[8] Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1207–17.
[9] Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195–206.
[10] Bronowicki J, Davis M, Flamm S, et al. Sustained virologic response (SVR) in prior pegInterferon/ribavirin (PR) treatment failures after retreatment with boceprevir (BOC)+ PR: PROVIDE study interim results. J Hepatol 2012;56(Suppl.):S6.
[11] Salomon J, Weinstein M, Hammitt J, Goldie S. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. JAMA 2003;290:228.
[12] Siebert U, Sroczynski G, Rossol S, et al. Cost effectiveness of peginterferon-2b plus ribavirin versus interferon-2b plus ribavirin for initial treatment of chronic hepatitis C. Gut 2003;52:425.
[13] Liu S, Cipriano LE, Holodniy M, et al. New protease inhibitors for the treatment of chronic hepatitis C. Ann Intern Med 2012;156:279–90.
[14] Bennett W, Inoue Y, Beck J, et al. Estimates of the cost-effectiveness of a single course of interferon-2b in patients with histologically mild chronic hepatitis C. Ann Intern Med 1997;127:855.
[15] Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol 2010;52:652–7.
[16] Thein H, Yi Q, Dore G, Krahn M. Estimation of stage specific fibrosis progression rates in chronic hepatitis C virus infection: a meta analysis and meta regression. Hepatology 2008;48:418–31.
[17] Benvegnu L, Noventa F, Bernardinello E, et al. Evidence for an association between the aetiology of cirrhosis and pattern of hepatocellular carcinoma development. Gut 2001;48:110.
[18] Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterol 1997;112:463–72.
[19] Gentilini P, Laffi G, La Villa G, et al. Long course and prognostic factors of virus-induced cirrhosis of the liver. Am J Gastroenterol 1997;92:66–72.
[20] Sangiovanni A, Prati GM, Fasani P, et al. The natural history of compensated cirrhosis due to hepatitis C virus: a 17 year cohort study of 214 patients. Hepatology 2006;43:1303–10.
[21] Serfaty L, Aumaître H, Chazouillères O, et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology 1998;27:1435–40.
[22] Bruno S, Silini E, Crosignani A, et al. Hepatitis C virus genotypes and risk of hepatocellular carcinoma in cirrhosis: a prospective study. Hepatology 1997;25:754–8.
[23] Tateyama M, Yatsuhashi H, Taura N, et al. Alpha-fetoprotein above normal levels as a risk factor for the development of hepatocellular carcinoma in patients infected with hepatitis C virus. J Gastroenterol 2011;46(1):92–100.
[24] Tsukuma H, Hiyama T, Tanaka S, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 1993;328:1797.
[25] Yoshida H, Shiratori Y, Moriyama M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. Ann Intern Med 1999;131:174.
[26] Planas R, Ballesté B, Antonio Álvarez M, et al. Natural history of decompensated hepatitis C virus-related cirrhosis: a study of 200 patients. J Hepatology 2004;40:823–30.
[27] Thuluvath P, Guidinger M, Fung J, et al. Liver transplantation in the United States, 1999–2008. Am J Transplant 2010;10:1003–19.
[28] Davis G, Alter M, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterol 2010;138:513–21.
[29] Lang K, Danchenko N, Gondek K, et al. The burden of illness associated with hepatocellular carcinoma in the United States. J Hepatol 2009;50:89–99.
[30] Saab S, Hunt DR, Stone MA, et al. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: a decision analysis model. Liver Transplant 2010;16:748–59.
[31] Wolfe R, Roys E, Merion R. Trends in organ donation and transplantation in the United States, 1999–2008. Am J Transplant 2010;10(4, part 2):961–72.
[32] Szeto KL, Devlin NJ. The cost-effectiveness of mammography screening: evidence from a microsimulation model for New Zealand. Health Pol 1996;38:101–15.
[33] Younossi Z, Singer M, McHutchison J, Shermock K. Cost effectiveness of interferon 2b combined with ribavirin for the treatment of chronic hepatitis C. Hepatology 1999;30:1318–24.
[34] McAdam-Marx C, McGarry LJ, Hane CA, et al. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: a managed care perspective. J Manag Care Pharm 2011;17:531–46.
[35] Davis KL, Mitra D, Medjedovic J, et al. Direct economic burden of chronic hepatitis C virus in a United States managed care population. J Clin Gastroenterol 2011;45:e17.
[36] Hanmer J, Lawrence WF, Anderson JP, et al. Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. Med Decis Making 2006;26:391–400.
[37] Wilson J, Yao G, Raftery J, et al. A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in

anaemia associated with cancer, especially that attributable to cancer treatment. Health Technol Assess 2007;11:1–202.
[38] Chong CAKY, Gulamhussein A, Heathcote EJ, et al. Health-state utilities and quality of life in hepatitis C patients. Am J Gastroenterol 2003;98:630–8.
[39] Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology 2001;34:809–16.
[40] Arias E. United States life tables, 2006. Nat Vit Stat Rep 2010;58:1.
[41] Centers for Medicare & Medicaid Services, HHS. Medicare program: changes to the hospital inpatient prospective payment systems and fiscal year 2008 rates. Fed Reg 2007;72:47129–8175.
[42] American Hospital Directory. Hospital statistics by state. Available from: http://www.ahd.com/state_statistics.html. [Accessed July 12, 2012].
[43] van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584–93.
[44] Poynard T, Colombo M, Bruix J, et al. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. Gastroenterol 2009;136:1618–28. e2.
[45] Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399–401.
[46] Poordad F, Bronowicki JP, Gordon SC, et al. Factors that predict response of patients with hepatitis C virus infection to boceprevir. Gastroenterol 2012;143:608–18. e1–5.
[47] Ghany MG, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;54(4):1433–44.
[48] Sulkowski M, Poordad F, Manns MP, et al. Anemia during treatment with peginterferon alfa-2b/ribavirin with or without boceprevir is associated with higher SVR rates: analysis of previously untreated and previous-treatment-failure patients. Gastroenterol 2011;140(Suppl.): S941–2.
[49] Cammà C, Petta S, Cabibbo G, et al. Cost-effectiveness of boceprevir or telaprevir for previously treated patients with genotype 1 chronic hepatitis C. J Hepatol 2013 May 23. pii: S0168-8278(13)00350-4. 10.1016/j.jhep.2013.05.019. In press.
[50] Ferrante SA, Chhatwal J, Brass CA, et al. Boceprevir for previously untreated patients with chronic hepatitis C genotype 1 infection: a US-based cost-effectiveness modeling study. BMC Infectious Dis 2013;13:190.
[51] Cammà C, Petta S, Enea M, et al. Cost-effectiveness of boceprevir or telaprevir for untreated patients with genotype 1 chronic hepatitis C. Hepatology 2012;56:850–60.